The role of Intermediate Respiratory Care Units in preventing ICU collapse during the COVID pandemic.

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Research

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The role of Intermediate Respiratory Care Units in preventing ICU collapse during the COVID pandemic.

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ABSTRACT

Introduction: There is limited information describing features and outcomes of patients requiring Intermediate Respiratory Care Unit (IRCU) hospitalization for COVID19 disease and as of yet, no mechanical or medical treatments have clearly demonstrated efficacy in IRCU.

Methods: Demographics and clinical variables on admission, as well as medical and mechanical therapeutic interventions, were extracted from Electronic Clinical Records in 274 SARS-CoV-2 infected patients attending a third level hospital IRCU. Using multivariate logistic regression analysis, variables that best discriminated mortality were obtained. Principal components analysis and a neural network (NN) algorithm were applied.

Results: In relation to respiratory support, high-flow oxygen therapy and weaning procedures were associated with survival as were CPAP and non-invasive ventilation with low levels of support among the most severely affected. The IRCU achieved a survival rate of 87.6%, avoided 178 ICU admissions, successfully referred 35% to the ICU, and of these, 94% later survived the weaning phase. Higher mortality incidence was associated with cardiac and respiratory diseases and fever, heart rhythm and blood pressure disturbances. Following analysis of specific therapeutic options Corticoids and Anticoagulants were associated with better outcomes.

Conclusions: The IRCU prevented the collapse of the ICU, allowed for recovered ICU patients to be quickly released from their unit, thus freeing up critical care beds and permitting them to function more effectively and in terms of mortality, achieved good results, that did not worsen due to a possible delay in intubation. In addition, we have generated an open-access NN capable of identifying severity predictors of SARS-CoV-2.

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Key Words: SARS-CoV-2 Pandemic; Neural Network; Artificial Intelligence; CPAP; NIMV; High Flow Oxygen; Cyclosporine; Tocilizumab; Corticosteroids

Introduction

During the current pandemic, the Intermediate Respiratory Care Unit (IRCU) dealt directly with patients suffering from very severe respiratory failure due to viral pneumonia caused by SARS-CoV-2. Four lines of respiratory therapies were applied: Continuous Positive Airway Pressure (CPAP), Non Invasive Mechanical Ventilation (NIMV) and High Flow Oxygen (HFO) in the acute phase and Invasive Mechanical Ventilation (IMV) during weaning.

We describe the IRCU's experience and results, which was able to quadruple its capacity in less than a week, while being attended by three 24-hour on-duty pulmonologists and supported by six more physicians from other specialties. Regulations and recommendations established through national consensus were followed when treating this entity¹

Regarding HFO systems, air mixing was quickly eliminated due to hypoxemia. But strict control of oxygen partial pressure was necessary to avoid hyperoxia² and to timely identify the existence of refractory shunts that would not respond to oxygen therapy³. New procedures were acquired from the ICU to help solve such extreme hypoxia, such as the prone position⁴ combined with HFO therapy or NIMV. Lower pressurization rates and pressure supports were used to avoid overventilation and volutrauma⁵injury (VILI).

Throughout this pandemic, weaning of some patients during the recovery phase has overlapped the hyperacute peak flow phase of acutely ill patients, and the IRCU had to quickly adapt to successfully face these two synchronous situations, implementing two different protocols of action at the same time, which required a high level of organization and excess demand upon medical and nursing staff.

The object of this study is to analyze mortality using direct statistical analysis based on logistic regression and predictive NN analysis. This article also illustrates patients' flow between the ICU and our highly specialized IRCU with more than 20 years of experience^{6, 7, 8}.

MATERIAL AND METHODS

Study Population

A total of 274 patients from January 1st 2020 to May 5th 2020 admitted to a third-level hospital IRCU were included. All patients had confirmed SARS-CoV-2 infection by a positive result upon polymerase chain reaction testing. The local clinical practice guide (**detailed in Table 1 supplemental**) was followed which includes the admission criteria in IRCU or ICU. De-identified medical records were confidentially collected from Microsoft Sql Integration Services (SSIS) reporting database and analyzed using R version 3.5.2 (R Project for Statistical Computing; R Foundation). Approval from the Institutional Ethics Committee was obtained. All methods were carried out in accordance with relevant guidelines and regulations.

Data Collection and baseline variables included in the study

Demographics, baseline comorbidities, vital signs, use of treatments, either mechanical or medical, and outcomes were extracted from clinical charts and manually revised.

Missing Data Imputation

Patients and parameters with a high percentage (>50%) of missing values were excluded from the analysis. In the remaining patients, missing data was imputed using KNN method (K=5).

Neural Network And Data Re-Sampling

The neural network (NN) model was built using the caret R package (<https://CRAN.R-project.org/package=caret>). We used the "nnet" method, and implemented an automatic selection of: i) the optimal number of units per hidden layer (1 to 5), and ii) the optimal value for the regularization parameter to avoid over-fitting (0.1 to 0.5 in increments of 0.1 units). We used the "twoClassSummary" method to compute sensitivity, specificity and the area under the ROC

curve. This NN algorithm was performed 10 times over a matrix of re-sampled patients. Re-sampled matrices were composed of patients with severe status (outcome = 1) and a random selection of the same number of patients with less severe status (outcome = 0). For each re-sampled matrix, we performed a 10-fold cross validation where 90% of patients we randomly used as the training dataset and the remaining (10%) as the testing dataset. A total of 100 NN models were performed and a ROC curve was calculated for the set of predictions and real values using 10-fold cross-validation. The final AUC, accuracy, sensitivity and specificity were calculated as the mean of the 100 NN models performed in total. Our R script is available at: <https://github.com/pminguez/MachineLearning4UnbalancedData/blob/master/nn4covid19.R>

Principal Component Analysis

Principal component analysis (PCA) was performed on the matrices with missing data imputation, centered and scaled, using the prcomp and factoextra R libraries. Ellipses represent 95% of the data. PCA analyses were performed over the same scenarios chosen to perform the NN.

Fisher exact test analysis

For binary type of variables, which included comorbidities, treatments and gender, odds ratios for each of the two severity classes in each comparison were calculated, contingency 2x2 tables were obtained and significance was calculated with 2-tailed Fisher test. P values were adjusted using FDR and adjusted p values <0.05 were taken as significant. Graphics were built sorting variables by relative odds ratios (1/odds ratio when <1).

Wilcoxon test analysis

For non-binary variables comprising vital signs, a non-parametric Wilcoxon rank sum test was performed over the set of values of each variable for the two severity states. P-values were

adjusted by FDR and $FDR < 0.05$ were considered as significant. Means of the two sets of values for each variable was calculated to assign a direction of the test.

Logistic Regression Classification based on comorbidities, vital signs and drug consumption

First, the univariate logistic regression models were obtained. Then, the best multivariable model was sought. For this, all possible models were adjusted, and the one with the lowest AIC value (Akaike Criterion) was chosen. Finally, the goodness of fit of the model was assessed (Hosmer and Lemeshow Test), and the ROC curve was obtained using the Leave One Out (LOO) cross-validation technique.

Analysis of the effect of mechanical devices on survival in this cohort of patients

Fisher's exact test was performed to investigate the association between the type of respiratory support and mortality. To compare the parameters used with the different techniques and their association with mortality, the student's t test was used. In all cases it was considered that there was statistical significance when $p < 0.05$. We applied our NN based algorithm to detect treatments predicting success or failure. The Fisher test was applied to binary data while Wilcoxon was used with continuous data.

Results

Cohort Description

Supplementary Figure 1 shows epidemiologic data, drugs used and comorbidities of the patients, while **Figure 1** describes the dataset, with a global mortality rate of 12,4%, 178 ICU admissions were avoided, 35% of IRCU patients required transfer to the ICU and of these, 96% of them later survived at weaning. Of the patients included, 20.8% were <50 years, 44.5% were between 50 and 70 and 34.3% were over 70 years old.

Mortality increased with age, reaching 32% in patients older than 70 years (Figure 1B). A day-to-day report of deaths (Figure 1C) and fortnite mortality (Figure 1D-E) illustrate a higher mortality rate at the beginning of the pandemic. Mortality reached it's maximum in early March amongst the elderly, and then progressively decreased, being clearly contained by early April.

Supplementary Figure 2 presents the Helmet cohort, showing Comorbidities, Biomarkers and global and Helmet vital signs.

Comorbidities associated with worst prognosis

We performed PCA and NN analyses over the 274 patients, classifying them into two states - deceased vs. alive or transferred to ICU - at the time of data collection. **Figure 2A** shows principal component (PC or dimension 1) against PC2. Cardiovascular affections and respiratory disorders were the conditions which most contributed to separation between states. Odds ratios of the different comorbidities further revealed that seven disease families were associated with fatal outcomes without enrichment. **Figure 2 B** show results for Ages between 50-70 years (123 patients) where tobacco consumption, cardiac and respiratory disease were most relevant, while for those older than 70 years (94 patients) **Figure 2C** respiratory and oncological disease seemed to be the most important comorbidities related to death. For the most severe patients

(n=130) transferred to ICU or dead, Hypertension, cardiac, respiratory or oncological disease show a trend contributing to separation between states with an AUC=0.66 (**Supplementary Figure 3**).

Univariate and multivariate regression analysis confirms the results obtained by the NN in the overall cohort (**Table 1**) and in the more severe patients (**Table 2**). The LOO-CV AUC for the logistic model was 0.73 (0.64, 1) for the overall cohort and the Hosmer-Lemeshow test reached $p = 1$. The LOO-CV AUC for the logistic model in the more severe was 0.53 (0.68, 0.62) and the Hosmer-Lemeshow test reached $p = 1$ for the more severe patients (**Supplementary Figure 4 A and B**). We note that all comorbidities were collected from electronic medical records without data associated with them in relation to the severity of the disease or the syndromic type.

Risk prediction by vital signs and their cut-off values

In relation to abnormal vital signs in the Emergency Department, heart rate and temperature were found to be the variables which best discriminated between deceased patients and survivors, according to PCA and NN analysis for all patients (**Figure 3A**). The NN was able to classify patients with an AUC=0.68, achieving a value of 0.83 when the classification was made in the 50-70 year range, where temperature, heart rate and systolic blood pressure (**Figure 3B**) were selected. Similar results were obtained in patients >70 years (**Figure 3C**). Results between deceased and ICU-admitted patients show relevance of bradycardia, hypothermia and arterial blood pressure (**Supplementary Figure 5**).

Univariate and multivariate regression analysis confirmed the results obtained by the NN with oxygen saturation being significant in the overall cohort (**Table 3**), as in more severe patients (**Table 4**). The LOO-CV AUC for the logistic model was 0.76 (0.76, 0.69) for the overall cohort and the Hosmer-Lemeshow test reached $p = 0.773$. The LOO-CV AUC for the logistic model in

the more severe was 0.83 (0.88, 0.67) and the Hosmer-Lemeshow test reached $p = 0.114$ for the more severe patients, **(Supplementary Figure 6 A and B)**.

Therapeutic modalities and patient survival

Medical Treatment

In the 50-70 year range, drugs associated with survival were Corticoids, Chloroquine, Lopinavir and Cyclosporine **(Figure 4A)**. Regarding those > 70 years **(Figure 4B)**, Corticoids, Betaferon and Anticoagulants show a trend associated with survival. We further explored the effect of drugs on survival in the most severe group of patients. Interestingly, PCA showed a clear separation between these categories and revealed a positive contribution of all specific drugs to survival. And the NN in this cohort show **(Figure 4C)**, with an AUC=0.88, that Corticoids, Enoxaparin, Acetylcysteine, Beta interferon, Tocilizumab, Lopinavir, and Cyclosporine were the compounds with greater capacity to classify patients. Enrichment analysis showed the benefit of these drugs, with high odds ratios and $FDR < 0.05$, along with Betaferon. NN in severe patients older than 70 years attain an AUC of 0.83 with similar results and a contribution of Anakinra to survival without enrichment **(Supplementary Figure 7)**.

It is important to highlight that both univariate and multivariate regression analysis confirm the results obtained by the NN in the overall cohort **(Table 5)** and in the more severe patients **(Table 6)**. The LOO-CV AUC for the logistic model was 0.65 (0.82, 0.76) for the overall cohort and the Hosmer-Lemeshow test reached $p = 1$. The LOO-CV AUC for the logistic model in the more severe was 0.91 (0.79, 0.92) and the Hosmer-Lemeshow test reached $p = 0.998$ for the more severe patients **(Supplementary Figure 8 A and B)**.

Respiratory Support Therapies

Regarding respiratory support, **Figure 5A** shows the use of support techniques, including Helmet, which was only used in 2.18% of the subjects. NIMV was used in 13.41%, CPAP in 23.7%, HFO in 40.5% and IMV, only for weaning, in 13.5%.. The rest of the patients were on Oxygen alone either by nasal cannula or mask. In general, given the high minute volumes of the patients, HFO was chosen as the initial therapy. When hypoxemia was refractory, a CPAP test was performed and maintained if recruitment improved hypoxemia. In case of a history of COPD, hypercapnia or previous use, NIMV with low levels of support pressure was used. Helmet was relegated to extreme situations. There is an association between the type of respiratory support and mortality. **Figure 5 B** shows the parameters used. Pressure Support and PEEP levels refer to NIMV through Helmet or full-face mask, CPAP levels refer to equipment capable of administering this mode of ventilation except Helmet. We must consider that two devices were used with the HFO: the Optiflow™ system (Fisher & Payckel Healthcare) where the air and oxygen flow was selected separately and Precision Flow^R (Vapotherm Inc) in which the total flow and FiO₂ were fixed. The Student's t-test **Figure 5 C** shows that the choice of parameters is related to survival. NN **Figure 6A** show that HFO and the tracheotomy weaning procedure that incorporated the use of a hemi-cannula with an AUC of 0.97 are associated with survival. In the cohort of severe patients older than 70 years **Figure 6B**, all techniques improved survival, being CPAP especially robust once its programming value is included and weaning. NIMV and HFO were also associated with survival and the only technique in this group of patients associated with mortality is Helmet ventilation, although it was only used in 6 patients. Oxygen alone, either through nasal cannula or mask weren't related to survival.

Discussion

The study demonstrates that IRCU admission did not worsen mortality and limited the demand for ICU resources. The IRCU prevented a collapse of the ICU, allowed it to quickly release patients so as to effectively return to normal, and achieved, considering the severity of lung injury, good results in terms of mortality, which did not increase because of a possible delay in intubation. Also, the present study illustrates the performance of a NN capable of identifying and classifying mortality predictors in SARS-CoV-2 infected patients that can be used in future mono or multicenter studies. Different statistical approaches were used in the treatment of data. The principal component analysis shows a photograph of the distribution of the variables, the logistic regression extracts those associated with survival, and the neural network selects those associated with survival with the greatest predictive power in a model designed to achieve self-learning and improve predictive capacity when increasing the size of the sample.

In the cohort, male subjects, as previously described⁹, were more frequently affected. Among those admitted, 12.4% died, considering survival (52.5%) and the possibility of transfer to the ICU (35%) as success. Normally, transfer to the ICU is a criterion of IRCU failure, but in this pandemic keeping the patient alive and well oxygenated until achieving an ICU bed was decisive. In fact, the patients referred to this unit returned for the most part to wean (80%) and 94% survived. 6% died in the ICU, so we can conclude that intubation was not ultimately delayed. In our ICU, all beds were finally able to dedicate to invasive support since the IRCU absorbed the non-invasive support in its entirety. If this had not been the case, it would have collapsed since the number of subjects treated at the UCRI far exceeded the available ICU beds. The reduction in mortality by early April may be likely due to better access to the ICU (**Figure 1E**), the use of weaning procedures without mortality, better organization, better use of the therapeutic guide and perhaps drugs associated with survival.

Regarding comorbidities, we detect that underlying diseases, including hypertension, respiratory, cardiovascular and oncological disease, may be risk factors for severe patients compared with non-severe patients^{10,11}. In general cohorts^{12,13,14}, the discriminating risk factors are hypertension, diabetes and neurological disorders. Although renal dysfunction seems to be protective according to the analysis of neural networks, the logistic regression rules it out (**Tables 1 and 2**).

In regard to vital signs, arterial blood pressure alterations, heart rate and temperature are better predictors of poor prognosis, as previously documented^{13,15}. The multivariate regression model selects hypoxemia and hyperoxia also. This underlines the importance of containing extreme saturations in this type of patient².

Regarding treatment, the institution was guided by a unified protocol. In almost all cases either with NN or Logistic Regression, with the limitations of this type of study, it is possible to glimpse a signal in favor of steroids, and anticoagulants were associated with survival, as indicated by other authors^{15,16,17,18,19, 20}, and among the youngest and most seriously ill, other compounds such as Lopinavir, Tocilizumab and Cyclosporine stood out, which has already been described in broader cohorts considering cytokine storm syndrome and immunosuppression^{15,21}. Corticosteroids are controversial in COVID-19 pneumonia in accordance with current WHO guidance²². However, in agreement with previous observations²³, we found that their combination with other drugs was consistently associated to a higher survival. Tocilizumab is currently undergoing a clinical trial, but data from a pilot study²⁴ suggests that it could have a beneficial effect. In severe cases, the role of Acetylcysteine stands out, probably improving the dense secretions and possibly having an antioxidant effect²⁵. The use of Cyclosporine A has been recently discussed²⁶. Our institution set up a randomized clinical trial assessing the efficacy of Cyclosporine as an add-on therapy to standard of care, which is now ongoing²⁷. All these conclusions regarding the advantages of one or the other treatments must be confirmed in randomized clinical trials in order to validate them.

During the pandemic, mortality in the IRCU has doubled its usual annual rate of around 6% while attending approximately 250 patients per year⁸. During this current crisis, the IRCU treated nearly 300 patients during a month and a half period.

With respect to Helmet, it was only used in 6 patients with a mortality of 100%. This was probably related to the decision of relegating this mask to the final stage of refractory extreme hypoxia. In **Supplementary Figure 2**, there are evident severity features of these patients compared to the general cohort. However, during this pandemic Helmet has been recommended as the first choice interface¹. It has been described to improve the prognosis in patients with ARDS²⁸ minimize aerosolization and dispersion of particles from the respiratory tract²⁹, as well as decrease the incidence of complications usually associated with other masks^{30,31,32}. In the institution, personnel have already been trained for a possible future wave in which this technique will be in the front line.

HFO has shown remarkable superiority in the cohort. In randomized controlled trials³³ HFO has been shown to improve survival in non-intubated patients by comparison with simple oxygen therapy or noninvasive ventilation. In this cohort, a poor evolution is clearly seen in subjects treated with O₂ only (O₂ Mask or reservoir bag) **Figure 6A**. As it has been described^{34, 35}, it reduces the ventilatory demand, the severity of dyspnea and the respiratory rate. In consequence it decreases risk of (P-SILI)⁵⁴.

Regarding CPAP, the current data shows an association with survival in the most severe patients. In COVID-19 patients, the recommendation of NIMV use is still being debated³⁶. It is included in the WHO³⁷, the Italian Thoracic Society³⁸ and the Respiratory Care Committee of the Chinese Thoracic Society³⁹ recommendations, but it is advised against in the European Society of Intensive Care Medicine and the Society of Critical Care Medicine⁴⁰. In a recent French retrospective observational study, the use of CPAP was associated with lower intubation rate,

particularly in patients with a do-not-intubate (DNI) decision⁴¹. Some studies even begin to recommend non-invasive support due to excess mortality from invasive ventilation⁴².

Increased respiratory drive observed in these patients often conducted to spontaneous tidal volumes above 9 ml/kg, which was associated with mortality⁴³, which in turn lead to a need to reduce pressure support and even restrict its use to COPD patients or ventilatory failure¹. The reduction of breathing rate and work of breathing after the introduction of NIMV, in order to avoid patient self-inflicted lung injury (P-SILI)^{44,45,46}, was closely monitored, and determined if sedation/neuromuscular blockade and invasive mechanical ventilation was needed.

Remarkably higher lung compliance in COVID-19 patients was observed, distinguishing it from other forms of ARDS⁴⁷. Lower support pressure levels were found to be protective, probably in relation to lower minute volume ventilation in the context of the aforementioned P-SILI.

Regarding weaning and decannulation of tracheostomized patients, the IRCU follows a specific protocol⁴⁸, in which a tracheal hemi-cannula is placed in most patients. Both extubated and tracheostomized patients were admitted following ICU discharge, allowing to quickly freeing up ICU beds and resources. All of these patients survived. Open tracheostomy was performed in all cases following COVID-19 recommendations⁴⁹. Delirium was a limitation during weaning⁵⁰, managed by progressively decreasing sedation as required, and once overcome, we followed the previously mentioned protocol, including a brief spontaneous breathing trial, progressive downsizing of the tracheostomy tube and increasingly longer periods of cuff deflation. A hemi-cannula was always employed to maintain access in case recannulation was required. After decannulation, 2 patients required recannulation, which was easily done thanks to the hemi-cannula. The average time until the hemi-cannula was removed was 4 +/- 2 days. Time till total decannulation was shorter than previously published by other groups⁵¹.

Regarding the limitations of this study, we should point out that the results of the neural network are not superior to those of the logistic regression, since this tool needs a larger cohort in order to learn and thus improve its predictive capacity. Despite this, the results it offers are confirmed by the logistical analysis. Additionally, it is a very useful tool in case it is used in multicenter cohorts. Also the study has no control braches, and use retrospectively observational data. This is a descriptive study, performed under a common clinical protocol of the entire hospital, in which it tries to identify variables that may have a greater relationship with a worse patient prognosis. Given the descriptive, retrospective, single-center nature of the study, no definitive conclusions can be drawn. These are indicative results that should be established under randomized clinical trials.

Conclusions

The IRCU prevented the collapse of the ICU without increasing mortality. IRCU risk factors associated with mortality were cardiorespiratory, hemodynamic alterations and fever, indicating a poorer prognosis. The therapeutic options, which offered the best results, were related to corticoids, anticoagulants and some antirheumatics. In our series, HFO and weaning are the procedures most related to survival, while CPAP and NIMV with a protective profile were able to contain mortality in the most severe cases. Mortality did not increase with the evident delay in intubation in those cases where it was not avoidable.

Tables

Supplementary Table 1. Inpatient clinical practice guidelines in COVID19 pneumonia
Jimenez Diaz Foundation University Hospital Quironsalud group.

Inpatient clinical practice guidelines in COVID19 pneumonia Jimenez Diaz Foundation University Hospital Quironsalud group					
v5, 9th April 2020					
HOSPITAL ADMISSION CRITERIA AT THE ER					
Moderate to severe pneumonia according to		CURB65 > 2 or PORT risk class > II SaO2 < 93%, RR > 20 or PaO2 < 65 mm Hg Diffuse bilateral crackles Bilateral infiltrates at Chest X Ray			
Mild pneumonia with additional risk factors		Age > 50 and any of the following: ischemic heart disease, hypertension, cancer, obesity, severe asthma, chronic pulmonary disease, chronic hepatic injury, immunosuppression			
Respiratory distress		CURB65+1 with lymphopenia < 800 cells/uL, ferritin > 500 ug/L, any of LDH, CK, D-dimer and Troponin-I above upper normal limit			
Sepsis		PaO2/FiO2 < 150			
Septic shock		Consider direct admission to ICU			
INPATIENT THERAPEUTIC GUIDANCE					
Respiratory severity level on admission		requirements for oxygen administration			
Oxygen supply with nasal cannula or Venturi mask	Yellow 1	≥ FiO2 35%			Methylprednisolone 40mg, 250 mg/day (for 3 days) followed by 40-60 mg/day (4th and 5th days)
	Yellow 2	40% ≤ FiO2 ≤ 60%			
	Yellow 3	FiO2 ≥ 60%			
Intermediate respiratory care unit	Orange 1	High flow nasal cannula with FiO2 < 50% or < 30 l/min	Antimicrobial therapy (AT) + antiviral drugs (AV) + hydroxychloroquine + cyclosporin A + LMWH + acetylsalicylic acid + cholecalciferol 50000 IU/week	Cyclosporin A	MP 250 mg/day on 1st day followed by 40-60 mg/day for 4-5 days (consider new 250 mg pulses instead of tocilizumab)
	Orange 2	High flow nasal cannula with FiO2 > 50% or > 30 l/min			Tocilizumab (400 mg, single dose) on 2nd day
	Orange 3	Noninvasive ventilation (NIV) with CPAP or Helmet			MP 250 mg/day (1 to 3 days) following tocilizumab administration
Intensive care unit	Red 1	Invasive ventilation with PaCO2/FiO2 ≥ 200			Tocilizumab (400 mg, single dose) on 1st day (consider anakinra 100 mg/ day i.v. as rescue therapy)
	Red 2	Invasive ventilation with PaCO2/FiO2 < 200			MP at sepsis schedule equivalent dose (consider pulses of 250 mg/ day as rescue therapy)
	Red 3	Invasive ventilation with PaCO2/FiO2 < 200 plus qSOFA ≥ 3 and/or multi organ failure			
NOTES					
Effectiveness of treatments		there is not enough scientific evidence showing efficacy of any of the therapeutic measures included in general guidelines for the management of COVID-19 pneumonia			
		While RCT are launched, adhesion to an internal clinical protocol facilitates extraction of real-world based data of safety and effectiveness of drugs			
ANTIBIOTICS					
First choice		Ceftriaxone 800/160 or Doxycycline 100 mg/12h for five days			
Comment		Macrolide use was claimed to be effective on decreasing viral load but data lack consistency. Additional antimicrobials may be used according to patient profile to manage concomitant infections.			
ANTIVIRAL DRUGS					
First choice		Lopinavir/ritonavir 200/50, 2 comp/12 h, Darunavir 800 mg/24 h + ritonavir 100 mg/24 h, Remdesivir 200 mg iv followed by 100 mg iv, day is restricted to severe / critically ill patients depending on availability.			
Comment		Problems of shortage, not proven effects, Limited to first week of symptoms, Remdesivir requires written informed consent			
CORTICOSTEROIDS					
Dose schedule		250 mg methylprednisolone daily pulses (1-3 days) as induction therapy to prevent rapid progression to respiratory distress, as rescue therapy after tocilizumab failure or in case of limitation of therapeutic efforts			
		Short course of methylprednisolone at the sepsis recommended schedule			
Comment		Use of corticosteroids remains controversial according to current literature although it could improve survival in critically ill patients. The rationale for their use as induction at first days of admission is to try to impair recruitment of inflammatory cells and hyper-production of inflammatory mediators, which can aggravate the condition.			
IMMUNOMODULATORS					
ANTI-MALARIALS					
First choice		Hydroxychloroquine 400 mg/12h 1st day, followed by 200 mg/12h, Chloroquine 500 mg/12h as an alternative			
Comment		Included in National Guidelines, No clear effect in available literature, Could low effectiveness, Risk of prolonged QT interval in combination (e.g. Azithromycin), Limited to first 5 days of admission			
CYCLOSPORIN A					
Dose schedule		Starting at 150 mg/day (< 60 kg weight), 150 mg/day (60 to 80 kg) and 200 mg/day (> 80 kg weight). Consider scaling dose after 4th to 150 mg/day, 200 mg/day and 300 mg/day, respectively. Individualised scaling thereafter.			
Comment		Written informed consent required, Data showing its ability to interfere with viral activity, Antiseprotic and cytoprotective effect in cell stress responses, Cost-effective, Rapid action, Easy to monitor side-effects, Avoid its use in stages 4-6 of chronic renal disease, Do not start if uncontrolled hypertension, Dose reduction in case of a 30% increase in serum creatinine, To be maintained during the whole process (2 to 3 weeks) if a clinical benefit is observed			
TOCILIZUMAB					
Administration criteria		Written informed consent required, Effective in short trials, A role in macrophage activation syndrome and also in acute respiratory failure associated to immunotherapy, CAPA-2, Problems of shortage, Use in progression after cyclosporin, severe interstitial pneumonia (AI), rapid progression requiring ventilatory support (N or R), extrapulmonary organ failure, mostly in case of a severe systemic inflammatory status as a reference, a threshold of 40 ng/ml for serum IL6 levels and of 420 ng/ml for D dimer are suggested, A second dose can be considered if partial response in individualised cases.			
Precautions		Avoid its use in case of increased procalcitonin levels or bacterial infections, hepatic failure, neutropenia (< 500 cells/uL), thrombocytopenia (< 50000 cells/uL), pregnancy, past history of diverticulitis, those patients with limitation of therapeutic efforts			
ANAKINRA					
Administration criteria		Written informed consent required, Failure to tocilizumab, instead of tocilizumab in fragile patients or in whom for other reasons may not be candidates to tocilizumab, non-desirable requirement of corticosteroids, 5 to 7 day courses.			
Precautions		Avoid its use in case of neutropenia (< 1500 cells/uL), Watch for local skin reactions.			
THROMBOPROPHYLAXIS					
First choice LMWH		Therapeutic dose	Intermediate dose	Prophylactic dose	
	Enoxaparin	1.5 mg/kg/24 h - 1 mg/kg/12 h	1 mg/kg/24 h	20 mg/24 h - 40 mg/24 h	
	Bemiparin	115 IU/kg/24 h	80 IU/kg/24 h	2500 IU/24 h - 3500 IU/24 h	
	Tinzaparin	175 IU/kg/24 h	100 IU/kg/24 h	3000 IU/24 h - 4500 IU/24 h	
Administration criteria		To any patient with pneumonia and thrombosis risk factors discharged at the ER (at standard prophylactic schedule) and to all hospital admitted patients. Dose adjustment to intermediate dosage in case of D-dimer > 3000. Individually consider intermediate or therapeutic dosage in D-dimer < 3000 if risk of bleeding is negligible. Maintain a prophylactic schedule for 7 to 10 days after discharge. Antithrombotic agents can be co-administered. For further indications including dose adjustments, use of tinzaparin and fondaparinux, or, pneumatic compression, clinicians are referred to the Hospital's thrombosis commission standard protocol and to on-call haematologist.			
		To avoid in case of thrombocytopenia (< 30000 cells/uL)			
First version launched on		16th March, 2020			
Approval from the 4 Public Quironsalud Hospitals Pharmacy committee on		26th March, 2020			
Principal revisions performed		26th March, 2020 Inclusion of MP pulses also in severity stages A1 and A2, Restriction of 2nd dose of tocilizumab 30th March, 2020 Increasing in thromboprophylaxis measures 3rd April, 2020 Inclusion of anakinra 6th April, 2020 Addition of acetylsalicylic acid and cholecalciferol 13th April, 2020 Inclusion of ruxolitinib, tocilizumab weight-based dose adjustment, information about ongoing CT			

Table 1**Comorbidities**

Exitus vs. rest 274 patients. Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Risk factor	UNIVARIABLE			MULTIVARIABLE ¹		
	OR	(95% CI)	P	OR	(95% CI)	P
Smoker	1.1	(0.56, 2.11)	0.784			
Cardiac_Disease	1.8	(0.86, 3.61)	0.116			
Pulmonary_Disease	1.82	(0.90, 3.58)	0.094	1.82	(0.90, 3.58)	0.094
Diabetes	1.12	(0.47, 2.42)	0.787			
Renal_Disease	0.59	(0.09, 2.18)	0.466			
Neurological_Disorder	1.68	(0.67, 3.87)	0.259			
Oncological_Disease	1.33	(0.36, 3.88)	0.639			
Hypertension	1.4	(0.73, 2.67)	0.309			

¹ Hosmer and Lemeshow test: p = 1

Table 2**Comorbidities**

Exitus vs. ICU 130 patients . Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Risk factor	UNIVARIABLE			MULTIVARIABLE ¹		
	OR	(95% CI)	P	OR	(95% CI)	P
Smoker	1.67	(0.72, 3.79)	0.229			
Cardiac_Disease	3.22	(1.21, 8.56)	0.020			
Pulmonary_Disease	2.73	(1.11, 6.62)	0.028	2.93	(1.08, 7.86)	0.034
Diabetes	1.52	(0.53, 4.06)	0.423			
Renal_Disease	0.94	(0.05, 7.63)	0.957	0.10	(0.00, 1.61)	0.111
Neurological_Disorder	2.51	(0.83, 7.37)	0.102			
Oncological_Disease	6.27	(1.16, 46.8)	0.033	15.3	(1.94, 321)	0.009
Hypertension	3.24	(1.45, 7.39)	0.004	2.99	(1.27, 7.19)	0.013

¹ Hosmer and Lemeshow test: p = 1

Table 3**Vital signs**

Exitus vs. rest 274 patients. Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Vital sign	UNIVARIABLE			MULTIVARIABLE ¹		
	OR	(95% CI)	P	OR	(95% CI)	P
First_Saturation	0.98	(0.94, 1.02)	0.309			
Min_Saturation	0.95	(0.93, 0.97)	<0.001	0.95	(0.92, 0.97)	<0.001
Max_Saturation	0.73	(0.61, 0.86)	<0.001	0.74	(0.58, 0.90)	0.001
First_SBP	1.00	(0.98, 1.01)	0.932	1.02	(1.00, 1.04)	0.050
Min_SBP	1.02	(0.98, 1.06)	0.257	0.98	(0.96, 1.00)	0.088
Max_SBP	1.01	(1.00, 1.01)	0.272	0.95	(0.89, 1.00)	0.063
First_DBP	0.98	(0.95, 1.00)	0.098			
Min_DBP	0.99	(0.97, 1.00)	0.042			
Max_DBP	0.95	(0.91, 0.98)	0.006			
First_Heart_Rate	1.00	(0.98, 1.01)	0.705			
Min_Heart_Rate	1.03	(1.00, 1.06)	0.039			
Max_Heart_Rate	1.01	(0.99, 1.03)	0.261	1.03	(1.01, 1.05)	0.011
First_Temperature	1.00	(0.70, 1.41)	0.993			
Min_Temperature	2.89	(1.42, 6.26)	0.003	2.16	(0.91, 5.41)	0.082
Max_Temperature	1.21	(0.83, 1.78)	0.321	1.51	(0.92, 2.50)	0.105

¹ Hosmer and Lemeshow test: p = 0.773

Table 4**Vital signs**

Exitus vs. ICU 130 patients . Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Vital sign	UNIVARIABLE			MULTIVARIABLE ¹		
	OR	(95% CI)	P	OR	(95% CI)	P
First_Saturation	0.99	(0.93, 1.05)	0.619			
Min_Saturation	0.93	(0.90, 0.96)	<0.001	0.95	(0.92, 0.98)	0.003
Max_Saturation	0.45	(0.30, 0.62)	<0.001	0.36	(0.21, 0.57)	<0.001
First_SBP	1.00	(0.98, 1.02)	0.928	1.04	(1.01, 1.07)	0.014
Min_SBP	1.05	(1.00, 1.11)	0.063	1.07	(0.98, 1.17)	0.139
Max_SBP	1.00	(0.99, 1.01)	0.530			
First_DBP	0.97	(0.94, 1.00)	0.022	0.94	(0.90, 0.98)	0.008
Min_DBP	0.99	(0.97, 1.01)	0.269			
Max_DBP	0.94	(0.90, 0.99)	0.014			
First_Heart_Rate	0.99	(0.96, 1.01)	0.362			
Min_Heart_Rate	1.02	(0.99, 1.06)	0.176			
Max_Heart_Rate	1.00	(0.98, 1.02)	0.941	1.04	(1.01, 1.07)	0.015
First_Temperature	0.73	(0.47, 1.10)	0.136			
Min_Temperature	2.44	(1.06, 6.11)	0.037			
Max_Temperature	0.63	(0.38, 1.01)	0.056			

¹ Hosmer and Lemeshow test: p = 0.114

Table 5**Drugs**

Exitus vs. rest 274 patients. Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Drug	UNIVARIABLE			MULTIVARIABLE¹		
	OR	(95% CI)	P	OR	(95% CI)	P
Amoxicillin	1.38	(0.48, 3.42)	0.524	2.35	(0.78, 6.36)	0.123
Azithromycin	2.19	(0.75, 5.77)	0.145			
Beta_Interferon	1.05	(0.49, 2.11)	0.900			
Ceftriaxone	0.69	(0.33, 1.36)	0.286			
Cloroquine_Hydroxychloroquine	0.94	(0.49, 1.79)	0.858			
Erythromycin	0.67	(0.19, 1.83)	0.462			
Levofloxacin	0.74	(0.37, 1.42)	0.364			
Lopinavir	1.03	(0.53, 2.05)	0.930			
Meropenem	1.33	(0.54, 3.00)	0.518			
Cyclosporine	1.06	(0.56, 2.02)	0.867			
Tocilizumab	0.93	(0.46, 1.81)	0.836			
Doxycycline	0.9	(0.47, 1.76)	0.758			
Dexamethasone	0.43	(0.16, 1.01)	0.052	0.30	(0.09, 0.76)	0.010
Methylprednisolone	1.31	(0.68, 2.59)	0.424			
Bemiparine	0.94	(0.49, 1.79)	0.858			
Enoxaparin	0.87	(0.45, 1.69)	0.675			
Tinzaparin	3.63	(0.89, 13.3)	0.069	6.78	(1.48, 31.0)	0.015
Anakinra	1.97	(0.42, 7.14)	0.354			
Acetylcysteine	0.68	(0.36, 1.32)	0.250			

¹ Hosmer and Lemeshow test: p = 1

Table 6**Drugs**

Exitus vs. ICU 130 patients. Univariate, Multivariate Logistic regression analysis and Hosmer and Lemeshow test.

Drug	UNIVARIABLE			MULTIVARIABLE¹		
	OR	(95% CI)	P	OR	(95% CI)	P
Amoxicillin	3.21	(0.94, 11.1)	0.063	13.6	(1.35, 174)	0.027
Azithromycin	0.83	(0.18, 2.93)	0.788			
Beta_Interferon	0.29	(0.10, 0.72)	0.007	0.06	(0.01, 0.43)	0.004
Ceftriaxone	0.45	(0.19, 1.03)	0.058			
Cloroquine_Hydroxychloroquine	0.56	(0.25, 1.24)	0.153	0.28	(0.05, 1.19)	0.086
Levofloxacin	0.8	(0.35, 1.78)	0.583			
Lopinavir	0.25	(0.11, 0.60)	0.002	7.96	(1.26, 67.2)	0.026
Meropenem	0.27	(0.07, 0.75)	0.010			
Cyclosporine	0.28	(0.12, 0.64)	0.003			
Tocilizumab	0.22	(0.09, 0.50)	<0.001	0.35	(0.08, 1.44)	0.143
Doxycycline	0.23	(0.10, 0.56)	0.001			
Dexamethasone	0.08	(0.02, 0.25)	<0.001	0.00	(0.00, 0.03)	<0.001
Methylprednisolone	1.2	(0.53, 2.83)	0.666	12.1	(2.11, 114)	0.004
Bemiparine	0.59	(0.26, 1.29)	0.186			
Enoxaparin	0.04	(0.01, 0.12)	<0.001	0.01	(0.00, 0.10)	<0.001
Tinzaparin	3.07	(0.69, 13.7)	0.136	34.5	(2.27, 1237)	0.010
Anakinra	0.45	(0.02, 2.80)	0.436			
Acetylcysteine	0.13	(0.05, 0.32)	<0.001			

¹ Hosmer and Lemeshow test: p = 0.998

FIGURE LEGENDS

Supplementary Figure 1. Demographics Analysis of 274 patients. **A)** Gender and Anthropometrics. **B)** Age Distribution **C)** Comorbidities. **D)** Drugs frequency used

Figure 1. Outcomes. Analysis of 274 patients. **A)** Outcomes **B)** Mortality related to age **C)** Daily number of Dead in IRCU **D)** Time sections mortality from March to May 2020. **E)** Admissions, ICU transfer and Mortality over time.

Supplementary Figure 2. Patients cohort using Helmet. **A)** Comorbidities and drug consumption **B)** Biomarkers **C)** Vital signs of the global cohort (274 patients) **D)** Vital signs of the Helmet cohort (6 patients)

Figure 2. Comorbidities in dead and non-dead admitted patients. Analysis of 274 patients. **A) all ages.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **B) 50-70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **C) >70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 3. Comorbidities in dead and ICU transferred patients. Analysis of 130 patients. **A) all ages.** PCA analysis, **B)** NN ROCs, **C)** importance in NN model, and **D)** Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 4. Logistic regression analysis Roc curve for comorbidities. **A)** overall population. **B)** More severe patients (dead and ICU transferred patients)

Figure 3. Vital Signs in dead and non-dead admitted patients. Analysis of 274 patients. **A) all ages.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **B) 50-70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **C) >70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 5. Vital Signs in dead and ICU transferred patients. Analysis of 130 patients. **A) all ages.** PCA analysis, **B)** NN ROCs, **C)** importance in NN model, and **D)** Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 6. Logistic regression analysis Roc curve for Vital Signs. **A)** overall population. **B)** More severe patients (dead and ICU transferred patients)

Figure 4. Drugs consumption in dead and non-dead admitted patients. **A) 50-70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **B) >70 years-old.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **C) all ages ICU transferred vs. dead.** PCA analysis, NN ROCs, importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 7. Drug consumption in dead and ICU transferred patients >70 years. Analysis of 37 patients. **A)** PCA analysis, **B)** NN ROCs, **C)** importance in NN model, and **D)** Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Supplementary Figure 8. Logistic regression analysis Roc curve for Vital Signs. **A)** overall population. **B)** More severe patients (dead and ICU transferred patients)

Figure 5. Respiratory Support demographics. **A)** Respiratory support in alive and dead. Fisher test. **B)** Parameters (mean and sd) used with every technique. **C)** Comparison between parameters related to respiratory support (t-student test)

Figure 6. Respiratory support in dead and non-dead admitted patients. **A) all ages.** PCA analysis, **B)** NN ROCs, **C)** importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$. **B) >70 years-old.** PCA analysis, **B)** NN ROCs, **C)** importance in NN model, and Fisher test results, sorted by relative odd ratios. Significance taken as $FDR < 0.05$.

Figures

Supplementary Figure 1.

Figure 1

Supplementary Figure 2

A

Helmet Comorbidity %	Hypertension	Respiratory Disease	Oncological Disease	Diabetes	Tobacco
	83,00	50	50	16,6	16,6
Helmet Cohort Drug %	Lopinavir	Beta Interferon	Cyclosporine	Tocilizumab	Esteroids
	100	50	75	16,6	33

B

HELMET	LEUCOCYTES	HEMOGLOBIN	PLATELETS	VSG	CREATININE	SODIUM	POTASSIUM	FERRITINE	IL6	CPK	D-DIMER	LDH
MEAN	15702,67	13,00	236187,17	119,67	0,58	131,33	4,30	1484,00	10,67	229,00	3512,67	864,33
Ds	2281,60	1,26	40336,69	34,60	0,16	2,58	0,57	247,04	3,50	130,73	1675,03	196,38

C

Vital Signs n= 274	Mean	Ds
First_Saturation	90,01	6,93
Min_Saturation	87,69	13,74
Max_Saturation	98,01	1,97
First_SBP	128,26	22,52
Min_SBP	103,76	13,66
Max_SBP	122,98	34,70
First_DBP	73,36	13,12
Min_DBP	64,91	26,30
Max_DBP	89,31	7,59
First_Heart_Rate	89,28	18,39
Min_Heart_Rate	58,87	13,05
Max_Heart_Rate	108,00	17,53
First_Temperature	37,03	2,42
Min_Temperature	34,64	5,22
Max_Temperature	37,86	2,44

D

Helmet vital Signs n=6	Mean	Ds
First_Saturation	86,3	5,8
Min_Saturation	79,5	5,1
Max_Saturation	97,3	1,5
First_SBP	138,3	11,3
Min_SBP	105,5	3,5
Max_SBP	167,8	12,7
First_DBP	60,8	5,3
Min_DBP	39,5	10,1
Max_DBP	75,5	7,9
First_Heart_Rate	75,8	6,9
Min_Heart_Rate	55,8	8,4
Max_Heart_Rate	120,8	23,5
First_Temperature	37,5	0,9
Min_Temperature	35,8	0,5
Max_Temperature	38,7	0,3

Figure 2

Supplementary Figure 3

Supplementary Figure 4

Figure 3

Supplementary Figure 5

ICU Transfer vs dead ALL AGES (130 patients)

Supplementary Figure 6

Figure 4

Supplementary Figure 7

ICU Transfer vs Dead 70-100 AGES (37 patients)

Supplementary Figure 8

Figure 5

Figure 6

DECLARATIONS

Ethics approval and consent to participate

This survey is a retrospective study using de-identified medical record data. No patient management protocols have been altered due to the study. The study was approved by the Institutional Ethics Committee, certificate 09/20 with nº EO085-20_FJD.

Availability of data and material

The datasets analyzed during the current study are available from the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests

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